First-in-Human Phase 1/2 Study of Tisotumab Vedotin in Advanced and/or Metastatic Solid Tumors

Johann S. de Bono[1], Nicole Concin[2], David S. Hong[3], Fiona C. Thistlethwaite[4], Jean-Pascal Machiels[5], Hendrik-Tobias Arkenau[6], Ruth Plummer[7], Robert Hugh Jones[8], Dorte Nielsen[9], Kristian Windfeld[10], Sri Ghatta[11], Brian M. Slomovitz[12], James F. Spicer[13], Jeffrey Yachnin[14], Martin David Forster[15], Reshma A. Rangwala[11], Ulrik Lassen[16]

[1]The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, London, UK; [2]BGOG and University of Leuven, Leuven Cancer Institute, Leuven, BE; [3]Phase I Unit, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [5]Department of Medical Oncology, Cliniques Universitaires Saint-Luc, Brussels, BE; [6]Sarah Cannon Research Institute, London, UK; [7]Sir Bobby Robson Cancer Trials Research Centre, Freeman Hospital, Newcastle, UK; [8]Velindre Cancer Centre and Cardiff University, Cardiff, UK; [9]Herlev Hospital, Oncology, Herlev, DK; [10]Genmab, Copenhagen, DK; [11]Genmab US, Inc., Princeton, NJ, USA ; [12]University of Miami, Oncology, Miami, USA; [13]King's College London, London, UK; [14]Karolinska University Hospital, Solna, SE; [15]University College London Hospitals, London, UK; [16]Department of Oncology, Phase 1 Unit, Rigshospitalet, Copenhagen, DK

Correspondence to: Johann de Bono, The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom. Phone: 44-20-8722-4028; Fax: 44-20-8642-7979;
E-mail: ku.ca.rci@onob-ed.nnahoj.

Running header: A Phase 1/2 Study of Tisotumab Vedotin in Solid Tumors

Abstract: 298/300

Manuscript body: 3335/3500

Tables and figures: 5

Supplemental tables and figures: 6

References: 24

ABSTRACT

Background. Tisotumab vedotin (TV; HuMax-TF-ADC), is a first-in-class antibody-drug conjugate directed against tissue factor (TF), which is expressed across multiple solid tumor types and is associated with poor clinical outcomes. We hypothesize that TV could have antitumor activity in tumors known to express TF.

Methods. This is a phase 1/2 open-label, dose-escalation and -expansion study (innovaTV201; NCT02001623) evaluating the safety, tolerability, pharmacokinetics (PK) profile, and antitumor activity of TV in patients with locally advanced and/or metastatic solid tumors known to express TF. In the dose-escalation phase, patients were treated with TV intravenously once every 3 weeks in a traditional 3 + 3 design to determine the maximum-tolerated dose (MTD) and recommended phase 2 dose (RP2D). Plasma was collected to characterize the PK profile of TV. In the dose-expansion phase, patients are treated at the RP2D in seven advanced solid tumor-type cohorts, including bladder, cervix, endometrium, esophagus, lung, ovary, and prostate cancers.

Findings. In the dose-escalation phase, 27 patients with advanced solid tumors received TV in eight sequential dose cohorts between 0·3 and 2·2 mg/kg. Dose-limiting toxicities, including grade 3 type 2 diabetes mellitus, mucositis, and neutropenic fever, were observed at TV 2·2 mg/kg. TV at 2·0 mg/kg was identified as the MTD and the RP2D. The PK profile of TV was dose proportional. In the dose-expansion phase, 147 patients with solid tumors were treated with TV at 2·0 mg/kg. The most common (≥20%) treatment-emergent adverse events (AEs) of any grade included epistaxis, fatigue, nausea, alopecia, conjunctivitis, decreased appetite, and constipation. Across tumor

types, the confirmed investigator-assessed overall response rate was 15·6% (95% CI: 10·2%-22·5%).

Interpretation. TV demonstrated a manageable safety profile with encouraging preliminary antitumor activity across multiple tumor types, in heavily pretreated patients. Based on these data, continued evaluation of this agent is needed.

Funding. Genmab A/S.

RESEARCH IN CONTEXT

Evidence before the study

We performed a search through August 9, 2018 to identify all clinical studies evaluating the use tissue factor (TF)-targeting therapeutics in patients with cancer. Our search included PubMed and used the following search terms: “tissue factor”, or thromboplastin or CD142 AND phase. TF is expressed by multiple solid tumor types and contributes to cancer biology by promoting metastasis, tumor growth and tumor angiogenesis, suggesting that it may be a potential target for therapeutic intervention. Our search revealed that no studies have been published on the safety and activity of TF-targeting agents in patients with cancer; although two early phase clinical trials evaluated agents in patients with macular degeneration or acute lung injury.

Added value of this study

To our knowledge, this is the first study assessing the safety, tolerability, pharmacokinetics, and preliminary activity of a TF-targeting agent, tisotumab vedotin (TV), in patients with cancer. In this phase 1/2 study, TV demonstrates a manageable safety profile and preliminary activity in patients with advanced solid tumors, including bladder, cervix, endometrium, esophagus, lung, and ovary.

Implications of all the available evidence

The prognosis for patients with advanced solid tumors remains poor and there is an unmet need for new treatments to improve outcomes. The present trial confirms the feasibility and preliminary clinical utility of tisotumab vedotin, a TF-targeting antibody drug conjugate, in patients with locally advanced and/or metastatic solid tumors known

to express TF. Further studies are required to confirm this activity and assess the patient populations in which TV is most likely to be effective.

INTRODUCTION

Tisotumab vedotin (TV) is a first-in-class antibody-drug conjugate (ADC) that is directed against tissue factor (TF) expressed on the cell surface of tumor cells to deliver a clinically validated toxic payload to tumors.[1] TV is comprised of a fully human monoclonal antibody specific for TF conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable valine-citrulline linker.[1]

TF is a transmembrane glycoprotein that functions as the main initiator of the extrinsic pathway of blood coagulation.[2] Beyond its function in coagulation, TF has cell-signaling properties.[3,4] In conjunction with protease-activate receptor 2, TF can induce an intracellular-signaling cascade that tumors can exploit to promote malignant-cell survival, tumor growth, angiogenesis, and metastasis.[3,4] The role of TF in cancer biology is underscored by its aberrant expression in a broad range of solid tumors, including gynecologic and genitourinary tumors, squamous cell carcinoma of the head and neck (SCCHN), lung, pancreas, gastrointestinal tract cancers and others.[5-11] The expression of TF is enhanced in cancer through oncogenic events, such as constitutive activation of the MAPK- and PI3K-signaling pathways, epithelial-to-mesenchymal transition, hypoxia-induced signaling, and loss of tumor suppressor genes.[2,12-14] TF expression levels have been associated with poor clinical outcomes and higher metastatic potential in multiple solid tumor types.[9,15,16] Treatment options for many of these solid tumors remain limited and, especially in the context of metastatic and refractory disease, are often hampered by poor efficacy and significant drug toxicities. There is an urgent unmet medical need for more effective and safe treatment alternatives for patients with these types of cancer. Given its differential expression in

many cancers as well as its role in cancer biology, TF is a rational target for the development of therapeutics to help address this unmet need and improve patient outcomes across a broad range of solid tumors.

The antibody moiety of TV was selected from a panel of monoclonal antibodies based on interfering with TF-dependent intracellular signaling but not the procoagulant activity of TF.[1] Upon binding of TF by TV, the resulting complex is internalized and trafficked to the lysosome where the linker is enzymatically cleaved, releasing MMAE within the targeted tumor cell.[1,17] Then MMAE binds to tubulin and disrupts microtubule polymerization, resulting in G2/M cell cycle arrest and apoptosis. As a cell-permeable molecule, MMAE can also diffuse into the tumor microenvironment where it might induce bystander killing of neighboring dividing cells.[1,17] These antitumor effects are further enhanced by the capacity of TV to activate innate immune cells.[1] The binding of TV to FcγRIIIa on adjacent natural killer cells can lead to antibody-dependent cellular cytotoxicity of TF-expressing tumor cells.[1,18] Additionally, TV has been shown to induce immunogenic cell death, which can activate innate and adaptive immune responses to tumor antigen. In preclinical studies, TV has demonstrated robust antitumor activity in in vitro and in vivo mouse models in multiple solid tumors, including bladder, prostate, lung, pancreas, ovarian, and cervical, which demonstrated differential expression of TF.[1]

These preclinical data led to the conduct of the first-in-human TV clinical trial: innovaTV 201 (NCT02001623), which evaluated the safety, tolerability, pharmacokinetics, and antitumor activity of TV in patients with locally advanced and/or metastatic solid tumors known to express TF are presented. The results of this trial are presented herein;

cancers known to express TF and with susceptibility to microtubule disrupting agents were evaluated.

PATIENTS AND METHODS

Patient Population

Eligible patients had locally advanced and/or metastatic cancer of the bladder, cervix, endometrium, esophagus, non-small cell lung cancer (NSCLC), ovary, prostate (in particular castration-resistant prostate cancer [CRPC]), or squamous cell carcinoma of the head and neck (SCCHN) (dose escalation only) who had failed or were not eligible to receive the available standard of care. Eligible patients were aged ≥18 years, had a life expectancy ≥3 months, acceptable organ function, hematologic and coagulation status, Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1·1.[19]

Patients were excluded if they had past or current coagulation defects, ongoing major bleeding, on long-term antiplatelet or anticoagulant therapy, clinically significant cardiac disease, major surgery within 6 weeks before drug infusion or anticipated during study treatment, open biopsy within 7 days before drug infusion, had another malignancy, or known infection with HIV, hepatitis B virus, or hepatitis C virus. Patients were also excluded if they had received prior therapy with an auristatin derivative, bevacizumab within 12 weeks from first study dose, radiotherapy within 28 days from first study dose, or any other anticancer therapy within five half-lives before first dose.

The Independent Ethics Committee (IEC) or Institutional Review Board (IRB) at each study site approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent for participation.

Study Design

This study was conducted as a phase 1/2, open-label, multicenter, dose-escalation and dose-expansion study. The primary objective of this study was to establish the safety and tolerability of TV. Secondary objectives were to establish the maximum-tolerated dose (MTD) of TV, to define the recommended phase 2 dose (RP2D), to characterize the pharmacokinetic (PK) profile of TV, and to assess the antitumor activity of TV.

The dose-escalation phase of this clinical trial was conducted using a traditional 3 + 3 design. Patients were enrolled to eight cohorts of TV, ranging from 0.3 to 2.2 mg/kg administered intravenously once every 3 weeks (1Q3W). The decision to proceed to the next dose-level in the dose-escalation phase was based on the rate of dose-limiting toxicities (DLT) observed during the first 21-day treatment cycle. If one of the three patients at a given dose developed a DLT, then an additional 3 patients were added at the same dose level. If none of the three patients, or one of six, developed a DLT then the study continued escalation to the next dose level. The dose level below the dose at which 2 or more DLTs within 6 patients was defined as the MTD. During the expansion phase, patients were enrolled in tumor-type cohorts and treated with TV at the RP2D. Patients were treated for up to four cycles or until disease progression. Patients with demonstrated clinical benefit, defined as stable disease or better, had the option to continue treatment for an additional eight cycles or until unacceptable toxicity.

This report includes data from the completed dose-escalation phase and the ongoing (data cutoff February 1, 2018) expansion phase of the innovaTV 201 study.

Safety Assessments

Adverse events (AEs) were assessed and reported at each visit according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4·03. Serious AEs (SAEs) were defined as any AE that was fatal or life-threatening, required an extended hospitalization, resulted in persistent or significant incapacity/dysfunction, was deemed medically important, or led to a congenital anomaly or birth defect. A data-monitoring committee (DMC) evaluated safety data during the study. Causality for DLTs was assessed by the investigators and sponsor in collaboration with the DMC.

Response Assessments

Tumor assessments by computed tomography, or alternatively by magnetic resonance imaging in patients allergic to iodine contrast or at the discretion of the investigator were performed at screening and every 6 weeks during the study. Tumor response was investigator assessed per RECIST version 1·1 criteria.

Pharmacokinetics

Blood samples for PK analysis were collected before and after the infusion at each cycle. Additional samples were collected during cycles 1 and 2 on day 1 (2 hours, 5 hours, and 12 hours after the end of the infusion) and on days 2, 8, and 15. PK parameters, including area under the concentration time curve ($AUC_{0\text{-}t}$), maximum concentration (C_{max}), and time to reach maximum concentration (t_{max}), were determined from the concentration-time data, where feasible, for TV and free MMAE by

noncompartmental analysis. The PK parameters were calculated separately for cycle 1 and cycle 2 of treatment with TV.

Statistical Analyses

The sample size of the dose-escalation phase was calculated as a maximum of 48 patients based on the 3 + 3 design with three to six patients in each dose cohort. The estimated sample size for the dose-expansion phase was 169 patients, which had an 82% power to detect an AE with a 1% incidence.

The full analysis population is comprised of patients who were exposed to study drug. This population was used for evaluation of all endpoints. Safety evaluations and PK parameters were summarized descriptively. For the efficacy analysis, the investigator-assessed objective response rate (ORR) was determined with the corresponding two-sided 95% exact binomial CI. The Kaplan-Meier (KM) method was used to calculate the median months for progression-free survival (PFS) and duration of response (DOR), which were presented along the two-sided 95% CI.

Role of the Funding Source

The funder designed the study in collaboration with a subgroup of investigators, managed the clinical trial database, including oversight of data collection, performed statistical analyses, and provided medical writing assistance. The corresponding author had full access to all the data in the study and had the final responsibility to submit for publication.

RESULTS

Patients

The dose-escalation phase enrolled 27 patients, with a mixed population of primary tumor types. Three patients were included in dose cohorts ranging from 0·3 to 2·0 mg/kg, while six patients were included in the 2·2-mg/kg dose cohort. The median age of patients was 62 (43-73) years. The median number of prior therapies was 3 (1-14). In the dose-expansion phase, 147 patients were included across seven tumor-type cohorts, including bladder (n=15), cervical (n=34), endometrial (n=14), esophageal (n=15), NSCLC (n=15), ovarian (n=36), and prostate (n=18). The median age of patients was 59 (21-79) years. The median number of prior therapies across tumor types ranged from 1·5 to 4·0. Patient characteristics are listed in **Table 1**. Patient enrollment and disposition are illustrated in **Figure 1**.

Safety

In the dose-escalation phase, all 27 patients received ≥1 dose of TV and were evaluable for DLTs. Three DLTs were identified in the 2·2-mg/kg dose cohort, including type 2 diabetes mellitus, mucositis, and neutropenic fever, all of which were grade 3. Based on these data, the MTD and RP2D were defined as 2·0 mg/kg. There were three deaths reported; none of which were considered related to study drug. Two patients included in the 0·3-mg/kg dose cohort died from disease progression; one patient (SCCHN) included in the 0·6-mg/kg dose cohort died from a pharyngeal tumor hemorrhage.

In the dose-expansion phase, 147 patients received ≥1 dose of TV and were evaluated for safety. The mean (standard deviation; SD) duration of treatment in these patients was 14·5 weeks. Across tumor types, the most commonly (occurring in ≥20% of patients) reported treatment-emergent AEs (TEAEs) of any grade were epistaxis (69·4%), fatigue (55·8%), nausea (52·4%), alopecia (43·5%), conjunctivitis (42·9%), decreased appetite (36·1%), constipation (35·4%), diarrhea (29·9%), vomiting (28·6%), peripheral neuropathy (22·4%), dry eye (21·8%), and abdominal pain (20·4%) (**Table 2**). Treatment-emergent grade ≥3 AEs occurred in 56·5% of patients; 40·8% were deemed related to study drug. The most commonly (occurring in >2% of patients) reported treatment-emergent grade ≥3 AEs were fatigue (9·5%), anemia (5·4%), abdominal pain (4·1%), hypokalemia (4·1%), conjunctivitis (3·4%), hyponatremia (3·4%), and vomiting (3·4%).

Treatment-emergent SAEs occurred in 45·6% of patients; 26·5% were deemed related to study drug. The most common treatment-emergent SAEs (occurring in >2% of patients) were vomiting (4·1%), abdominal pain (3·4%), and anemia (2·7%) (**Table S2**). There were six AEs with fatal outcomes in the dose-expansion phase: two patients with general physical health deterioration, one with disease progression, one with metastasis to the central nervous system, one with esophageal metastatic cancer, and one with pneumonia. These events were deemed not related to study drug, with the exception of pneumonia, which was possibly related.

AEs of special interest included bleeding-related events, neuropathy, and ocular events (conjunctivitis, ulceration, keratitis, symblepharon). Epistaxis was the most commonly reported AE, the majority of which were grade 1 in severity. No grade 4-5 bleeding

events were reported in the dose-expansion phase. Neuropathy of any grade occurred in 42·9% of patients with 6·8% of patients experiencing grade ≥3 neuropathy (**Table S3**). The median (SD) time to onset of neuropathy was 8·7 (0·1-26·4) weeks. In patients who experienced neuropathy, 81% (51 of 63 patients) had received prior taxane chemotherapy, the most common of which was paclitaxel. At the time of this analysis, 15·9% (10 of 63) of neuropathy events had resolved, including seven patients with prior taxane, and 84·1% (53 of 63) of patients had ongoing symptoms, of which 44 patients received prior taxane. Ocular events of any grade occurred in 60% of patients, with conjunctivitis being the most common. Three percent of patients experienced grade ≥3 ocular events (**Table S4**). The study protocol was amended to implement ocular preventive measures, including the use of lubricating eye drops throughout the study period, steroid eye drops during the first 3 days of each treatment cycle, local ocular vasoconstrictor use before infusion, and cooling eye masks worn during treatment infusion, as well as stricter dose adjustment guidance. These mitigation strategies substantially reduced the incidence of conjunctivitis, which decreased from 55·8% to 28·6% (**Table S4**).

Pharmacokinetics and Blood Coagulation Parameters

The PK profile of TV was assessed in the dose-escalation phase. The profiles of mean blood concentration for TV and free MMAE are presented in **Figure S1**. Increases in exposure to TV and free MMAE were proportional to dose. The C_{max} of TV occurred shortly after the end of infusion, whereas levels of free MMAE peaked 1-2 weeks following infusion. Only low levels of free MMAE were detected in the systemic circulation. Parameters reflecting exposure, including C_{max} and $AUC_{0\text{-}t}$, increased

proportionally over the dose ranges examined (**Table S5**). When TV was dosed at 2·0 mg/kg (n=3), the mean C_{max} value was 1256·4 µg/mL and the mean AUC_{0-t} value was 32·3 h·µg/mL. Following a single-dose administration of TV at 2·0 mg/kg, time-to-peak plasma concentration (t_{max}) was observed 1·2 hours from the start of the infusion.

Blood coagulation parameters, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), were not altered by treatment with TV. Across dose-escalation cohorts, the mean (SD) PT value at baseline was 11·5 (1·3) seconds (n=18) compared with 11·7 (1·5) seconds (n=17) at study completion, while the mean (SD) aPTT value at baseline was 28.2 (3·3) seconds (n=25) compared with 27·1 (3.2) seconds (n=23) at study completion.

Efficacy

In the dose-escalation phase, 26 of the 27 patients were evaluable for response, with one patient with metastatic cervical cancer achieving a partial response (antitumor activity reported in **Table S6**). This patient had received two prior treatment lines before study entry and received TV at 1·2 mg/kg. In the dose-expansion phase, 128 of 147 patients were evaluable for investigator-assessed response. Nineteen patients were excluded because they did not have at least one on-study response evaluation. Across tumor types, the confirmed ORR for the full analysis population was 15·6% (95% CI: 10·2%-22·5%; 23 of 147 patients). All responses were partial. For each tumor type, the ORR was 26·7% (95% CI: 7·8%-55·1%) in bladder, 26·5% (95% CI: 12·9%-44·4%) in cervical, 13·3% (95% CI: 1·7%-40·4%) in esophageal, 13·9% (95% CI: 4·7%-29·5%) in ovarian, 13·3% (95% CI: 1·7%-40·5%) in NSCLC, 7·1% (95% CI: 0·2%-33·9%) in endometrium, and 0 in prostate (**Table 3**). At 12 weeks, the disease control rate (SD or

better) for all evaluable patients was 26·5% (95% CI: TBD%; 39 of 147 patients). Maximum percentage change in tumor size for each dose-expansion cohort is shown in **Figure 2**. Across tumor types, the median confirmed DOR was 5·7 (3·0-9·5) months and the median PFS was 3·0 (2·8-4·1) months.

Commented [CP1]: Note: to be updated

DISCUSSION

This multicenter, first-in-human clinical trial has validated the targeting of TF for the treatment of advanced cancer for the first time, and has shown that TV has an important antitumor activity in heavily pretreated patients with multiple different tumors known to express TF. The safety profile of TV 2·0 mg/kg 1Q3W was generally consistent with other MMAE-based ADCs, although epistaxis and conjunctivitis were reported at increased incidences with TV. Ocular toxicities have been reported with ADCs that include ravtansine (DM4) and monomethyl auristatin F (MMAF); however, they are rarely described for ADCs that utilize MMAE.[20] An ocular mitigation plan was implemented during the study that reduced the frequency and severity of ocular AEs, including conjunctivitis. Similar ocular mitigation strategies have been used prophylactically with other ADCs to manage ocular events. Peripheral neuropathy, a known toxicity of MMAE-based ADCs, was observed in patients treated with TV; however, most events reported were mild to moderate in severity. Three DLTs were reported in the 2·2-mg/kg dose cohort of the dose-escalation phase, one of which was type 2 diabetes mellitus. Hyperglycemia has been previously described as a DLT in other MMAE-based ADCs, such as brentuximab vedotin and DMOT4039A, and is likely to be due to the cytotoxic payload.[21,22]

This trial validates the use of an ADC-based approach to safely target TF, the main initiator of the extrinsic pathway of blood coagulation.[2] Coagulation parameters, such as PT and aPTT, were not affected by TV administration. Furthermore, despite the incidence of grade 1-2 epistaxis in 69·4% of patients receiving TV, no grade 4-5 bleeding events were observed in patients in the dose-expansion phase. These findings corroborate previous nonclinical toxicology studies of TV in cynomolgus monkeys, which demonstrated no significant impact on functional bleeding time or systemic parameters of coagulation at doses up to 5 to 6 mg/kg.[1]

Although not designed or powered to assess antitumor activity, this trial reports encouraging antitumor activity for TV in a broad population of patients with heavily pretreated, locally advanced and/or metastatic cancers of the bladder, cervix endometrium, esophagus, lung, and ovary. Patients with bladder and cervical cancer achieved the highest response rates with TV, with confirmed investigator-assessed response rates of 26·7% and 26·5%, respectively. Biopsy or archived samples were collected at study entry for all patients, and a currently ongoing analysis will assess the correlation of tumor TF expression and the antitumor activity of TV.

These data support the further investigation of TV. Multiple studies are underway, including innovaTV 207 and innovaTV 204. The former (NCT03485209) is an ongoing phase 2 study evaluating the efficacy, safety, and tolerability of TV monotherapy administered every 3 weeks in patients with relapsed, locally advanced or metastatic colorectal cancer, NSCLC, pancreatic cancer, or SCCHN.[23] The latter (NCT03438396) is an ongoing phase 2 study evaluating the efficacy, safety, and tolerability of TV

monotherapy in patients with previously treated, recurrent or metastatic cervical cancer that had progressed during or after treatment with standard first-line therapy.[24]

CONTRIBUTORS

Commented [CP2]: Note to be updated

DECLARATION OF INTERESTS

Commented [CP3]: Note to be updated

ACKNOWLEDGMENTS

We thank the patients, their families, and all of the investigators who participated in the study. Financial support for the study was provided by Genmab A/S. Medical writing and editorial assistance, under the guidance of the authors, was provided by Cindy Puente, PhD and Nancy Lerner-Weiss of Ogilvy CommonHealth and funded by Genmab A/S.

DATA SHARING

Commented [CP4]: Note: to be update

References

1. Breij EC, de Goeij BE, Verploegen S, et al. An antibody-drug conjugate that targets tissue factor exhibits potent therapeutic activity against a broad range of solid tumors. *Cancer research.* 2014;74(4):1214-1226.
2. van den Berg YW, Osanto S, Reitsma PH, Versteeg HH. The relationship between tissue factor and cancer progression: insights from bench and bedside. *Blood.* 2012;119(4):924-932.
3. Kasthuri RS, Taubman MB, Mackman N. Role of tissue factor in cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2009;27(29):4834-4838.
4. Zhang Y, Deng Y, Luther T, et al. Tissue factor controls the balance of angiogenic and antiangiogenic properties of tumor cells in mice. *The Journal of clinical investigation.* 1994;94(3):1320-1327.
5. Ohta S, Wada H, Nakazaki T, et al. Expression of tissue factor is associated with clinical features and angiogenesis in prostate cancer. *Anticancer research.* 2002;22(5):2991-2996.
6. Akashi T, Furuya Y, Ohta S, Fuse H. Tissue factor expression and prognosis in patients with metastatic prostate cancer. *Urology.* 2003;62(6):1078-1082.
7. Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2007;13(10):2870-2875.
8. Uno K, Homma S, Satoh T, et al. Tissue factor expression as a possible determinant of thromboembolism in ovarian cancer. *British journal of cancer.* 2007;96(2):290-295.
9. Patry G, Hovington H, Larue H, Harel F, Fradet Y, Lacombe L. Tissue factor expression correlates with disease-specific survival in patients with node-negative muscle-invasive bladder cancer. *International journal of cancer.* 2008;122(7):1592-1597.
10. Yokota N, Koizume S, Miyagi E, et al. Self-production of tissue factor-coagulation factor VII complex by ovarian cancer cells. *British journal of cancer.* 2009;101(12):2023-2029.
11. Cocco E, Varughese J, Buza N, et al. Expression of tissue factor in adenocarcinoma and squamous cell carcinoma of the uterine cervix: implications for immunotherapy with hI-con1, a factor VII-IgGFc chimeric protein targeting tissue factor. *BMC cancer.* 2011;11:263.
12. Rao B, Gao Y, Huang J, et al. Mutations of p53 and K-ras correlate TF expression in human colorectal carcinomas: TF downregulation as a marker of poor prognosis. *Int J Colorectal Dis.* 2011;26(5):593-601.
13. Milsom CC, Yu JL, Mackman N, et al. Tissue factor regulation by epidermal growth factor receptor and epithelial-to-mesenchymal transitions: effect on tumor initiation and angiogenesis. *Cancer research.* 2008;68(24):10068-10076.
14. Rong Y, Post DE, Pieper RO, Durden DL, Van Meir EG, Brat DJ. PTEN and hypoxia regulate tissue factor expression and plasma coagulation by glioblastoma. *Cancer research.* 2005;65(4):1406-1413.
15. Nitori N, Ino Y, Nakanishi Y, et al. Prognostic significance of tissue factor in pancreatic ductal adenocarcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2005;11(7):2531-2539.
16. Regina S, Valentin JB, Lachot S, Lemarie E, Rollin J, Gruel Y. Increased tissue factor expression is associated with reduced survival in non-small cell lung cancer and with mutations of TP53 and PTEN. *Clin Chem.* 2009;55(10):1834-1842.
17. de Goeij BE, Satijn D, Freitag CM, et al. High turnover of tissue factor enables efficient intracellular delivery of antibody-drug conjugates. *Mol Cancer Ther.* 2015;14(5):1130-1140.

18. Seidel UJ, Schlegel P, Lang P. Natural killer cell mediated antibody-dependent cellular cytotoxicity in tumor immunotherapy with therapeutic antibodies. *Frontiers in immunology.* 2013;4:76.
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
20. Donaghy H. Effects of antibody, drug and linker on the preclinical and clinical toxicities of antibody-drug conjugates. *mAbs.* 2016;8(4):659-671.
21. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(18):2190-2196.
22. Weekes CD, Lamberts LE, Borad MJ, et al. Phase I study of DMOT4039A, an antibody-drug conjugate targeting mesothelin, in patients with unresectable pancreatic or platinum-resistant ovarian cancer. *Mol Cancer Ther.* 2016;15(3):439-447.
23. ClinicalTrials.gov. Efficacy and safety study of tisotumab vedotin for patients with solid tumors. https://clinicaltrials.gov/ct2/show/NCT03485209. Accessed.
24. ClinicalTrials.gov. A trial of tisotumab vedotin in cervical cancer. https://clinicaltrials.gov/ct2/show/NCT03438396. Accessed.

FIGURE LEGENDS

Figure 1. Patient enrollment and disposition in innovaTV 201 (dose escalation and expansion)

Figure 2. Maximum reduction in tumor size in the various expansion study cohorts recruiting patients with (A) bladder, (B) cervix, (C) endometrium, (D) esophagus, (E) NSCLC, (F) ovary, and (G) prostate cancers.

The black bars indicate tumor size at first scan, and the gray bars indicate best response.

*Persistent nontarget lesions. †Percent change from baseline is 287·5%.

Table 1. Patient Characteristics

Characteristic	Dose Escalation	Dose Expansion
Total patients, No.	27	147
Age, median (range), y	62 (43-73)	59 (21-79)
Female, No. (%)	18 (67)	101 (69)
Race		
White	27 (100)	136 (92·5)
Black	0	2 (1·4)
Asian	0	4 (2·7)
Other	0	3 (2·0)
Missing	0	2 (1·4)
ECOG PS, No. (%)		
0	13 (48)	60 (40·8)
1	13 (48)	86 (58·5)
Missing	1 (4)	1 (0·7)
Primary tumor type, No. (%)		
Bladder	2 (7)	15 (10·2)
Cervix	2 (7)	24 (23·1)
Endometrium	3 (11)	14 (9·5)
Esophagus	4 (15)	15 (10·2)
NSCLC	4 (15)	15 (10·2)
Ovary	7 (26)	36 (24·5)
Prostate	4 (15)	15 (10·2)
SCCHN	1 (4)	–
Number of prior therapies, median (range)		
All	3 (1-14)	3 (1-9)
Bladder	–	2 (1-5)
Cervix	–	2 (1-5)
Endometrium	–	1.5 (1-5)
Esophagus	–	2 (1-4)
NSCLC	–	2 (1-5)
Ovary	–	4 (2-9)
Prostate	–	4 (3-7)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; PS=performance status; SCCHN= squamous cell carcinoma of the head and neck.

Table 2. TEAEs (Occurring in >10% of Patients) in the Dose-Expansion Phase

Preferred term	Dose Expansion Phase (n=147)			
	All Grade	Grade 1	Grade 2	Grade 3
Any AE, No. (%)	147 (100·0)	146 (99·3)	140 (95·2)	78 (53·1)
Epistaxis	102 (69·4)	100 (68·0)	2 (1·4)	0
Fatigue	82 (55·8)	28 (19·0)	40 (27·2)	14 (9·5)
Nausea	77 (52·4)	43 (29·2)	31 (21·1)	2 (2·0)
Alopecia	64 (43·5)	23 (15·6)	41 (27·9)	0
Conjunctivitis	63 (42·9)	21 (14·3)	37 (25·2)	5 (3·4)
Decreased appetite	53 (36·1)	34 (23·1)	17 (11·6)	2 (1·4)
Constipation	52 (35·4)	34 (23·1)	16 (10·9)	2 (1·4)
Diarrhea	44 (29·9)	28 (19·0)	14 (9·5)	2 (1·4)
Vomiting	42 (28·6)	26 (17·7)	11 (7·5)	5 (3·4)
Neuropathy peripheral	33 (22·4)	24 (16·3)	7 (4·8)	2 (1·4)
Dry eye	32 (21·8)	24 (16·3)	8 (5·4)	0
Abdominal pain	30 (20·4)	12 (8·2)	12 (8·2)	6 (4·1)
Weight decreased	25 (17·0)	6 (4·1)	19 (12·9)	0
Dyspnea	24 (16·3)	12 (8·2)	9 (6·1)	2 (1·4)
Pruritus	22 (15·0)	16 (10.9)	6 (4·1)	0
Hypokalemia	22 (15·0)	12 (8·2)	4 (2·7)	6 (4·1)
Rash	22 (15·0)	18 (12·2)	3 (2·0)	1 (0·7)
Myalgia	22 (15·0)	15 (10·2)	7 (4·8)	0
Arthralgia	21 (14·3)	12 (8·2)	9 (6·1)	0
Insomnia	21 (14·3)	14 (9·5)	6 (4·1)	1 (0·7)
Anemia	20 (13·6)	4 (2·7)	8 (5·4)	8 (5·4)
Back pain	19 (12·9)	11 (7·5)	7 (4·8)	1 (0·7)

Cough	18 (12·2)	16 (10·9)	2 (1·4)	0
Headache	17 (11·6)	12 (8·2)	5 (3·4)	0
AST increased	17 (11·6)	10 (6·8)	6 (4·1)	1 (0·7)
Peripheral sensory neuropathy	16 (10·9)	8 (5·4)	5 (3·4)	3 (2·0)
Pyrexia	15 (10·2)	12 (8·2)	1 (0·7)	1 (0·7)
ALT increased	15 (10·2)	6 (4·1)	7 (4·8)	2 (1·4)

*No grade 4-5 events were reported for TEAEs occurring in >10% of patients.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; TEAE=treatment-emergent adverse event.

Table 3. Antitumor Activity in the Dose-Expansion Phase

Response Evaluation*	All (n=147)	Bladder (n=15)	Cervix (n=34)	Endometrium (n=14)	Esophagus (n=15)	NSCLC (n=15)	Ovary (n=36)	Prostate (n=12)
ORR, No. (%) (95% CI)	23 (15·6) (10·2-22·5)	4 (26·7) (7·8-55·1)	9 (26·5) (12·9-44·3)	1 (7·1) (0·2-33·9)	2 (13·3) (1·7-40·4)	2 (13·3) (1·7-40·4)	5 (13·9) (4·7-29·5)	0
DCR, No. (%) (95%CI)	39 (26·5) (TBD)	5 (33·3) (TBD)	15 (44·1) (TBD)	4 (28·6) (TBD)	1 (6·7) (TBD)	2 (13·3) (TBD)	9 (25·0) (TBD)	3 (25·0) (TBD)

Commented [CP5]: Note: to be updated to include data based on full analysis population

*Confirmed responses per RECIST, per investigator review.

Abbreviations: DCR=disease control rate; ORR=overall response rate.

Figure 1. Patient enrollment and disposition in innovaTV 201 (dose escalation and expansion)

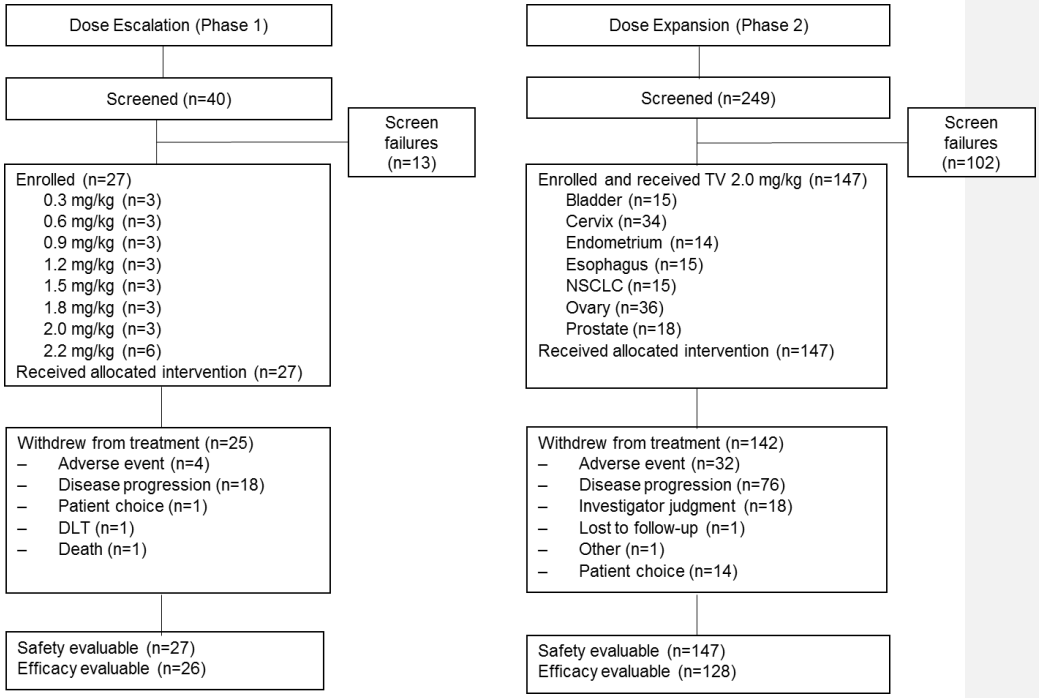
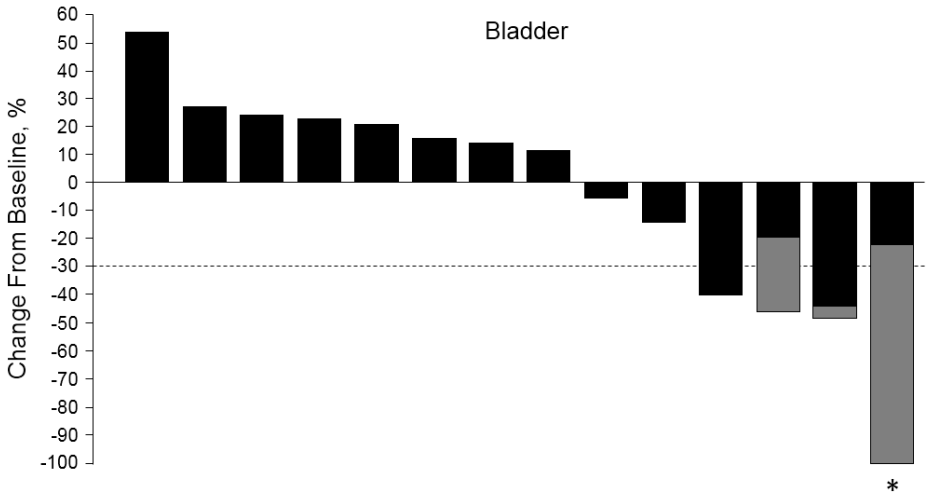
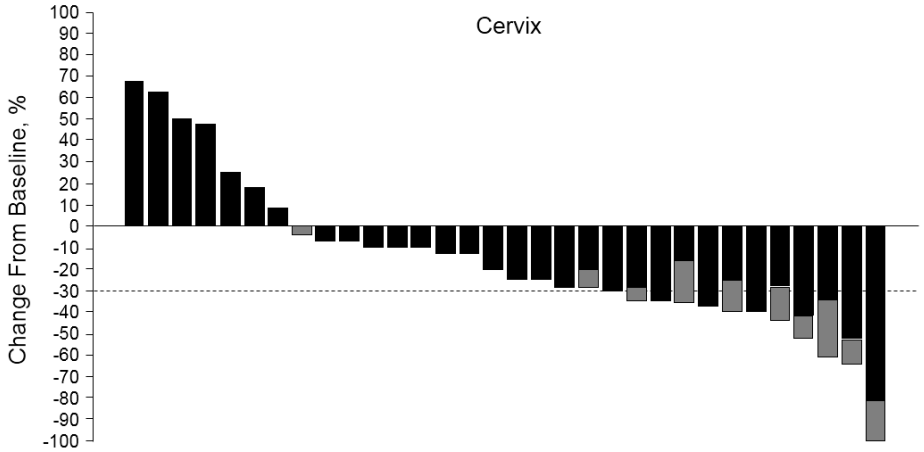


Figure 2. Maximum percentage reduction in tumor size in the various expansion study cohorts recruiting patients with (A) bladder, (B) cervix, (C) endometrium, (D) esophagus, (E) NSCLC, (F) ovary, and (G) prostate cancers.

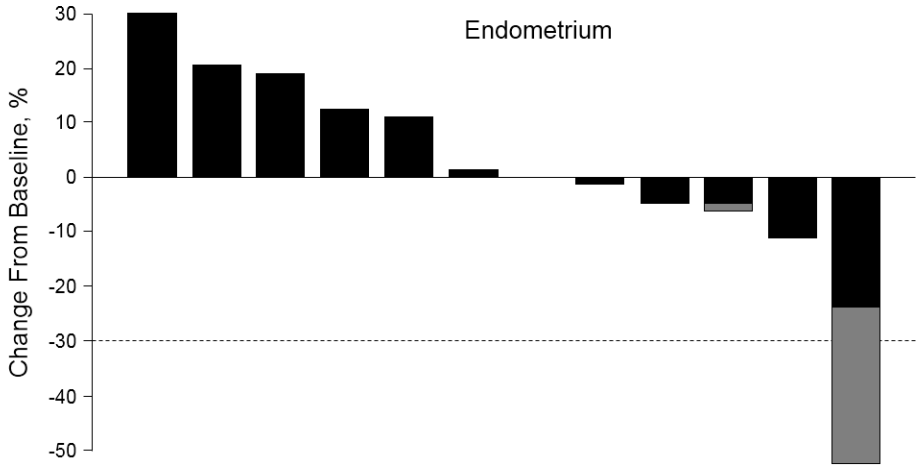
2A



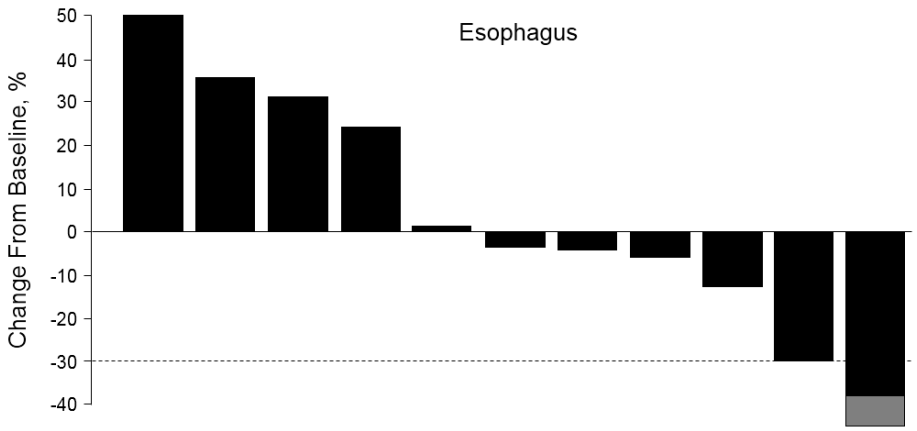
2B


Cervix
Change From Baseline, %
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100

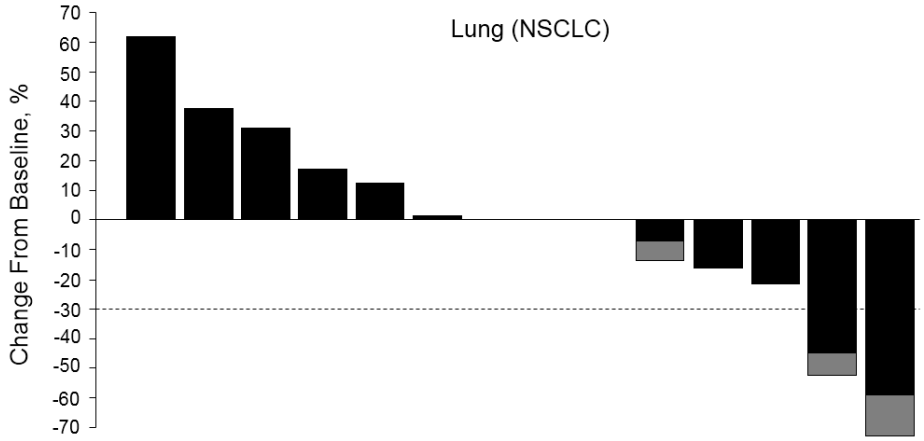
2C


Endometrium
Change From Baseline, %
30
20
10
0
-10
-20
-30
-40
-50

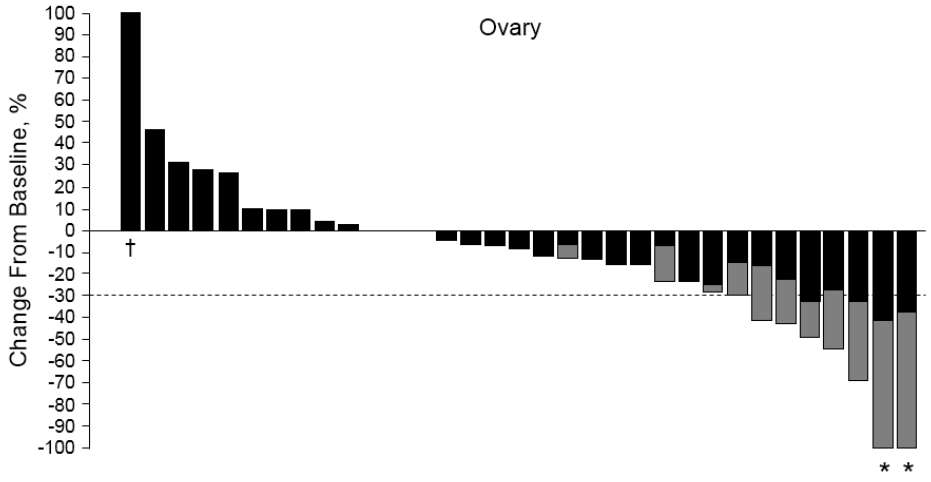
2D


Esophagus
Change From Baseline, %
50
40
30
20
10
0
-10
-20
-30
-40

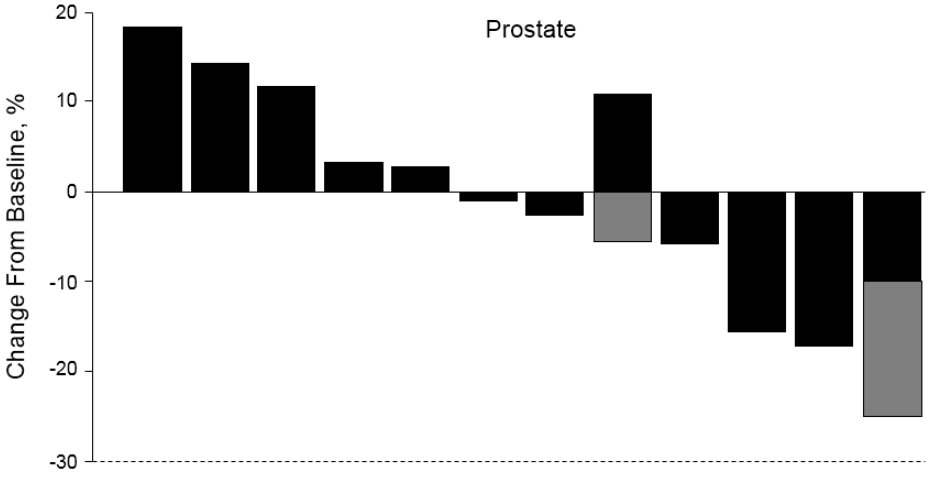
2E


Lung (NSCLC)
Change From Baseline, %
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70

2F


Ovary
Change From Baseline, %
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
†
* *

2G


Prostate
Change From Baseline, %
20
10
0
-10
-20
-30

First-in-Human Phase 1/2 Study of Tisotumab Vedotin in Advanced and/or Metastatic Solid Tumors

Johann S. de Bono[1], Nicole Concin[2], David S. Hong[3], Jean-Pascal Machiels[5], Fiona C. Thistlethwaite[4], Hendrik-Tobias Arkenau[6], Ruth Plummer[7], Robert Hugh Jones[8], Dorte Nielsen[9], Kristian Windfeld[10], Sri Ghatta[11], Brian M. Slomovitz[12], James F. Spicer[13], Jeffrey Yachnin[14], Martin David Forster[15], Reshma A. Rangwala[11], Ulrik Lassen[16]

[1]The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, London, UK; [2]BGOG and University of Leuven, Leuven Cancer Institute, Leuven, BE; [3]Phase I Unit, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [5]Department of Medical Oncology, Cliniques Universitaires Saint-Luc, Brussels, BE; [6]Sarah Cannon Research Institute, London, UK; [7]Sir Bobby Robson Cancer Trials Research Centre, Freeman Hospital, Newcastle, UK; [8]Velindre Cancer Centre and Cardiff University, Cardiff, UK; [9]Herlev Hospital, Oncology, Herlev, DK; [10]Genmab, Copenhagen, DK; [11]Genmab US, Inc., Princeton, NJ, USA ; [12]University of Miami, Oncology, Miami, USA; [13]King's College London, London, UK; [14]Karolinska University Hospital, Solna, SE; [15]University College London Hospitals, London, UK; [16]Department of Oncology, Phase 1 Unit, Rigshospitalet, Copenhagen, DK

Supplementary Information

Patient Inclusion and Exclusion Criteria

Eligible patients had locally advanced and/or metastatic cancer of the bladder, cervix, endometrium, esophagus, non-small cell lung cancer, ovary, prostate (in particular castration-resistant prostate cancer [CRPC]), or squamous cell carcinoma of the head and neck (dose escalation only) who had failed or were not eligible to receive the available standard of care. Eligible patients were aged ≥18 years, had a life expectancy ≥3 months, acceptable organ function, hematologic and coagulation status, Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to Response Evaluation Criteria in Solid Tumors version 1·1.[1] However, patients with CRPC could be included based on prostate-specific antigen (PSA) and/or bone metastases according to the Prostate Cancer Working Group Guideline; and patients with ovarian cancer could be included based on CA 125 positivity according to the Gynecologic Cancer Intergroup Guideline.[2,3]

Patients were excluded if they had past or current coagulation defects, ongoing major bleeding, on long-term antiplatelet or anticoagulant therapy, clinically significant cardiac disease, major surgery within 6 weeks before drug infusion or anticipated during study treatment, open biopsy within 7 days before drug infusion, had another malignancy (except for ≤stage 1B cervical carcinoma, prostate cancer with PSA ≤0·1 ng/mL, breast cancer in *BRCA1/2*+ ovarian cancer patients, noninvasive basal cell or squamous cell skin carcinoma, noninvasive superficial bladder cancer, or any curable cancer with complete response of >5 years), or known infection with HIV, hepatitis B virus, or hepatitis C virus. Patients were also excluded if they had received prior therapy with an auristatin derivative, bevacizumab within 12 weeks from first study dose, radiotherapy

within 28 days from first study dose, or any other anticancer therapy within five half-lives before first dose.

Dose-Limiting Toxicities (DLTs)

DLTs included the following adverse events (AEs) at least possibly related to TV:

- Grade 4 neutropenia for minimal duration of 7 days
- Grade 3 and 4 febrile neutropenia
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with bleeding episodes
- Major bleeding
- Stevens Johnson syndrome, toxic epidermal necrolysis, grade ≥3 cutaneous vasculitis
- Grade 3 neuropathy (not improving to grade 1 within 3 weeks following stop of dosing) and grade 4 neuropathy
- Grade 3 infusion-related AEs that do not resolve to grade 1 or baseline within 24 hours
- Grade 4 infusion-related events including anaphylaxis
- Any grade ≥3 nonhematologic AEs, which occur during the first treatment cycle and are at least possibly study drug related, excluding nonhematologic laboratory abnormalities that have no clinical consequences and resolve within 48 hours
- Grade ≥3 diarrhea and/or vomiting persisting for more than 48 hours with optimal medical management
- Grade ≥3 nausea (not disease-related) lasting 3 days or more with optimal medical management

Patient Recruitment

Patients were recruited across 3 sites (Denmark [n=1]; United Kingdom [n=1], United States [n=1]) for the dose-escalation portion and 21 sites (Belgium [n=6]; Denmark [n=2]; Sweden [n=1]; United Kingdom [n=9]; United States [n=3]) for the expansion portion.

Table S1. Treatment-Emergent SAE (Occurring in >1% of Patients) in the Dose-Expansion Phase

Preferred term	**Dose Expansion Phase (n=147)**
Any serious AE, No. (%)	67 (45·6)
Vomiting	6 (4·1)
Abdominal pain	5 (3·4)
Anemia	4 (2·7)
Hematuria	3 (2·0)
Constipation	3 (2·0)
Diarrhea	3 (2·0)
General physical health deterioration	3 (2·0)
Hyponatremia	3 (2·0)
Infection	3 (2·0)
Malaise	2 (1·4)
Vaginal hemorrhage	2 (1·4)
Colitis	2 (1·4)
Conjunctivitis	2 (1·4)
Dysphagia	2 (1·4)
Febrile neutropenia	2 (1·4)
Hypokalemia	2 (1·4)
Lower respiratory tract infection	2 (1·4)
Metastases to central nervous system	2 (1·4)
Nausea	2 (1·4)
Pneumonia	2 (1·4)
Sepsis	2 (1·4)
Urinary tract infection	2 (1·4)

Abbreviations: AE=adverse event; SAE=serious adverse event.

Table S2. Incidence of Neuropathy AEs in the Dose-Expansion Phase

Preferred term	Dose Expansion Phase (n=147)	
	All Grade	Grade ≥3
Any neuropathy event, No. (%)	63 (42·9)	10 (6·8)
Neuropathy peripheral	33 (22·4)	2 (1·4)
Peripheral sensory neuropathy	16 (10·9)	3 (2·0)
Muscular weakness	12 (8·2)	1 (0·7)
Peripheral motor neuropathy	5 (3.4)	1 (0·7)
Paresthesia	4 (2·7)	0
Polyneuropathy	4 (2·7)	2 (1·4)
Dysesthesia	3 (2·0)	0
Gait disturbance	2 (1·4)	0
Hypoesthesia	2 (1·4)	0
Demyelinating polyneuropathy	1 (0·7)	1 (0·7)
Guillain-Barré syndrome	1 (0·7)	0
Muscular atrophy	1 (0·7)	0

Abbreviation: AE=adverse event.

Table S3. Incidence of Ocular AEs in the Dose-Expansion Phase

Preferred term	All Patients (n=147)		Before mitigation (n=77)		After mitigation (n=70)	
	All Grade	Grade ≥3	Patients	AEs, No.	Patients	AEs, No.
Any ocular event, No. (%)[a]	88 (59·9)	5 (3·4)	50 (64·9)	85	38 (54·3)	79
Conjunctivitis	63 (42·9)	5 (3·4)	43 (55·8)	59	20 (28·6)	31
Dry eye	32 (21·8)	0	13 (16·9)	15	19 (27·1)	20
Conjunctival ulcer	6 (4·1)	0	1 (1·3)	1	5 (7·1)	5
Conjunctival hyperemia	4 (2·7)	0	0	0	4 (5·7)	5
Conjunctival scar	4 (2·7)	0	1 (1·3)	1	3 (4·3)	3
Keratitis	4 (2·7)	0	1 (1·3)	2	3 (4·3)	3
Noninfective conjunctivitis	4 (2·7)	0	1 (1·3)	1	3 (4·3)	3
Conjunctival hemorrhage	3 (2·0)	0	3 (3·9)	5	0	0
Symblepharon	3 (2·0)	0	0	0	3 (4·3)	3
Conjunctival disorder	2 (1·4)	0	0	0	2 (2·9)	3
Seasonal allergy	2 (1·4)	0	1 (1.3)	1	1 (1·4)	1

Conjunctival staining	1 (0·7)	0	0	0	1 (1·4)	1
Conjunctivitis allergic	1 (0·7)	0	0	0	1 (1·4)	1

Abbreviation: AE=adverse event.

[a]Most patients with conjunctivitis experienced other ocular events.

Table S4. PK Parameters of TV by Dose Cohort After a Single Dose

Dose level (mg/kg)	Patients, No.	AUC_{0-t}		C_{max}		T_{max}	
		Mean (h·μg/mL)	CV (%)	Mean (μg/mL)	CV (%)	Mean (h)	CV (%)
0·3	3	4·8	12·4	59·2	3·1	1·5	72·4
0·6	3	12·2	9·5	368·4	8·2	1·2	13·0
0·9	3	19·8	17·3	601·9	16·9	1·3	11·8
1·2	3	34·7	18·5	1084·7	9·3	1·2	11·7
1·5	3	23·1	21·1	795·0	19·0	1·1	9·6
1·8	3	35·4	39·2	1504·8	49·5	1·2	14·3
2·0	3	32·3	22·1	1256·4	33·1	1·2	7·5
2·2	6	55·5	10·3	2037·1	33·7	1·1	12·5

Abbreviations: AUC_{0-t} = area under the concentration time curve; C_{max}=maximum concentration; CV=coefficient of variation; PK=pharmacokinetic; t_{max}=time to reach maximum concentration.

Table S5. Antitumor Activity by Dose Cohort in the Dose-Escalation Phase

Response Evaluation*	All Doses (n=27)	0.3 mg/kg (n=3)	0.6 mg/kg (n=3)	0.9 mg/kg (n=3)	1.2 mg/kg (n=3)	1.5 mg/kg (n=3)	1.8 mg/kg (n=3)	2.0 mg/kg (n=3)	2.2 mg/kg (n=6)
PR, No. (%)	1 (3·7)	0	0	0	1 (33·3)	0	0	0	0
SD, No. (%)	11 (40·7)	0	1 (33·0)	1 (33·3)	1 (33·3)	0	3 (100)	1 (33·3)	4 (66·7)
PD, No. (%)	14 (51·9)	3 (100.0)	1 (33·0)	2 (66·7)	1 (33·3)	3 (100)	0	2 (66·7)	2 (33·3)
NE,† No. (%)	1 (3·7)	0	1 (33·0)	0	0	0	0	0	0

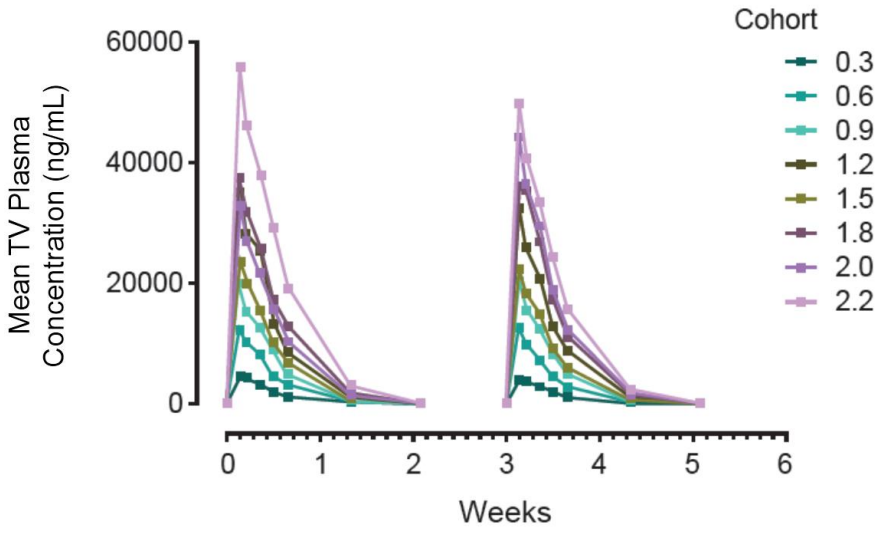
*Confirmed responses per RECIST, per investigator review. †Patient died prior to first scan.

NE=not evaluable; PD=progressive disease; PR=partial response; RECIST= Response Evaluation Criteria in Solid Tumors; SD=stable disease.

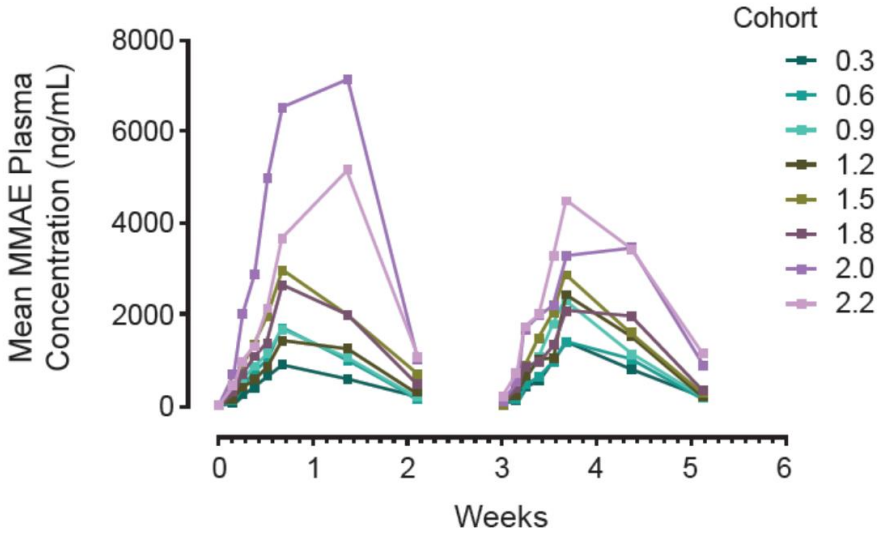
Figure S1. Mean plasma concentration-time profiles for (A) TV and (B) free MMAE at cycles 1 and 2, by dose-escalation cohort

Commented [CP6]: Note: Mean plasma concentrations to be regraphed for publication; units will be updated

1A



1B



References

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
2. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(7):1148-1159.
3. Rustin GJ, Quinn M, Thigpen T, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *Journal of the National Cancer Institute.* 2004;96(6):487-488.